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The 0.2-μg/day Fluocinolone Acetonide Intravitreal Implant in Chronic Noninfectious Posterior Uveitis

A 3-year Randomized Trial in India

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Objective: To examine the long-term efficacy and safety of the intravitreal 0.2-μg/day fluocinolone acetonide implant (FAi) to treat noninfectious uveitis (NIU) of the posterior segment (PS).

Design: Three-year, phase III, multicenter, randomized, double-masked, controlled, prospective study (clinicaltrials.gov, NCT02746991).

Participants: Overall, 153 patients in India with NIU-PS in ≥ 1 eye (with or without anterior uveitis) for ≥ 1 year who had ≥ 2 separate recurrences of uveitis requiring ocular injections or systemic therapy in the prior 12 months.

Methods: Patients were randomized 2:1 for baseline FAi or sham injection and monitored for main outcome measures.

Main Outcome Measures: Incidence and timing of uveitis recurrence, use of adjunctive therapy, best-corrected visual acuity, central foveal thickness, and monitoring of intraocular pressure (IOP)- and cataract-related events over 36 months.

Results: Overall, 153 patients (FAi, n = 101; treated sham, n = 52) were enrolled. Fluocinolone acetonide implant-treated eyes had significantly reduced uveitis recurrence rates versus treated sham (46.5% vs. 75.0%, respectively; $P = 0.001$) and a longer median time to recurrence (1116.0 [95% confidence interval, 847.00 to not evaluable] vs. 190.5 [95% confidence interval, 100.0–395.0] days for treated sham). Systemic adjunctive treatments were similar between groups, but fewer FAi-treated eyes required adjunctive injections (8.9% vs. 51.9% for treated sham). Visual outcomes were similar between groups, and residual macular edema was more common at 36 months in treated sham versus FAi-treated eyes (46.2% vs. 24.2%, respectively). The FAi-treated group had a lower central foveal thickness from month 12 onward. Intraocular pressure-lowering surgeries were stable in both groups, but, as expected, rates of IOP elevations were more frequent in the FAi-treated group than in the treated sham (IOP > 25 mmHg: 23.8% vs. 3.8%; IOP > 30 mmHg: 16.8% vs. 1.9%, respectively), and FAi-treated eyes had a higher incidence of cataract surgery than the treated sham (70.5% vs. 26.5%, respectively).

Conclusions: In patients with NIU-PS, the 0.2-μg/day FAi is associated with reduced-uveitis recurrence and increased time to first recurrence while controlling macular edema, maintaining stable IOP levels, and providing an expected safety profile, including a higher occurrence of cataract formation over 36 months.

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Noninfectious uveitis (NIU) affecting the posterior segment (PS) constitutes 15% to 22% of all cases of uveitis. Treatment of NIU is often a challenge because of the need to ensure that therapeutic levels of drug are delivered to the PS of the eye.[1] Noninfectious uveitis typically starts at a relatively young age and continues throughout life, often leading to burdensome costs related to hospital appointments, surgeries, and ultimately loss of vision if not properly managed.[2] Treatment goals for NIU-PS include controlling inflammation, minimizing recurrences, and preventing sight-threatening complications.[1]

Currently, the management of NIU-PS includes local administration of corticosteroids (topical, intra- or peri-ocular, or intravitreal [IVT]) and systemic administration of steroids or immunosuppressants. Topical corticosteroids may not be as effective for NIU-PS due to the limited intraocular penetration of most topical formulations. Peri-ocular and IVT injections are limited by duration of effect (approximately 6

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months, maximum) and the need for frequent retreatment.[3] In a study that compared the effectiveness of 3 regional corticosteroid injections for uveitic macular edema—peri-ocular triamcinolone acetonide, IVT triamcinolone acetonide, and the dexamethasone (DEX) IVT implant (OZURDEX, Allergan, Inc)—IVT triamcinolone acetonide and the DEX IVT implant were superior to peri-ocular triamcinolone acetonide for treating uveitic macular edema, with a modest increase in the risk of intraocular pressure (IOP) elevation that did not significantly differ between IVT injections.[4] Systemic administration of corticosteroids for NIU-PS is limited by systemic side effects and may not be a practical long-term option for many patients.[5] In a study by the Multicenter Uveitis Steroid Treatment Trial Research Group that compared systemic corticosteroid therapy with the 0.59-mg fluocinolone acetonide IVT implant (RETI-SERT, Bausch and Lomb), it was found that the implant maintained an advantage in controlling inflammation through 54 months in patients with intermediate, posterior, or panuveitis.[6]

In patients with chronic NIU-PS, an extended-release, lower-dose IVT corticosteroid implant may be preferable to either the surgically administered 0.59-mg fluocinolone acetonide implant (FAi) or short-duration IVT corticosteroids.[7] The IVT 0.2-μg/day FAi has been previously shown to provide stable, low-dose, and long-term release of fluocinolone acetonide.[8] The 0.2-μg/day FAi is indicated in Europe for diabetic macular edema and NIU-PS (ILUVIEN, Alimera Sciences Europe, Ltd),[9] while a 0.18-mg FAi is indicated in the United States for NIU-PS (YUTIQ, Alimera Sciences).[10] The phase II Fluocinolone Acetonide in Human Aqueous study demonstrated that eyes receiving the low-dose FAi maintained stable fluocinolone acetonide levels for $>$ 36 months. Steady-state aqueous levels of drug were achieved approximately 6 months after administration and were in the range of 1.0 ± 0.5 ng/ml.[8] Additionally, a parallel registration study demonstrated that the 0.2-μg/day FAi was efficacious in reducing the recurrence of NIU-PS $>$ 36 months.[11] To better understand post-FAi changes in NIU-PS disease state and treatment regimens as well as patient outcomes, the present clinical study examined the 36-month efficacy and safety of the 0.2-μg/day FAi versus sham control for the treatment of NIU-PS in India.

Methods

In this 3-year, phase III, multicenter, double-masked, controlled, prospective study (clinicaltrials.gov: NCT02746991), patients with NIU-PS were randomized 2:1 to treatment with the 0.2-μg/day FAi or sham control (sham injection followed by standard therapies as indicated, at the discretion of investigators; termed "treated sham" throughout). Administration of the 0.2-μg/day FAi was administered using a preloaded investigational study applicator similar to the injector used with the 0.18-mg FAi. In the sham injection procedure, the investigator used an empty 1-ml syringe with a blunt-end, 14-gauge needle pressed against the eye. The study was designed to evaluate the safety and efficacy of the 0.2-μg/day FAi in the management of patients with chronic NIU-PS versus treated sham. The study was conducted at 15 sites in India. The institutional review board at each center approved the study; these institutional review boards were located at LV Prasad Eye Institute (Hyderabad, India), Sri Sankaradeva Nethralaya (Guwahati, India), Regional Institute of Ophthalmology (Patna, India), CH Nagri Eye Hospital (Ahmedabad, India), King Edward Memorial Hospital and Seth Gordhandas Sunderdas Medical College (Mumbai, India), Deenanath Mangeshkar Hospital and Research Center (Pune, India), PBMA's HV Desai Eye Hospital (Pune, India), Dr. Shroff`s Charity Eye Hospital (New Delhi, India), Sankara Nethralaya (Chennai, India), Vasan Eye Care Hospital (Chennai, India), Sri Ramachandra Hospital (Chennai, India), JL Rohatgi Eye Hospital (Kanpur, India), King George's Medical University (Uttar Pradesh, India), ICARE Eye Hospital & Post Graduate Institute (Noida, India), and the Regional Institute of Ophthalmology (Kolkata, India). The study was performed in accordance with the Declaration of Helsinki, and all patients provided written informed consent before enrollment.

Inclusion criteria have been previously described.[12] The patients included in this study were diagnosed with unilateral or bilateral recurrent NIU-PS for $\geq$ 1 year before randomization, had received previous treatment for uveitis, and had uveitis recurrences that required treatment. Details of the study design were also previously discussed[11] and are summarized in Figure 1.

Sample size calculations and randomization and masking procedures were previously described.[12] Briefly, the total sample size of 150 patients was based on a 2-group continuity-corrected chi-square test with a 0.05 2-sided significance level and 95% power to detect the difference between a treated sham group recurrence-free rate of 0.600 and an FAi-treated group recurrence-free rate of 0.880 (odds ratio: 0.205) when the sample sizes were 50 and 100, respectively. For masking, one investigator performed the injection and day 1 evaluations, and another performed all future assessments.

The primary outcome measure was the difference in proportion of eyes in the FAi and treated sham groups that had uveitis recurrence within 6 months. The secondary outcome was the difference in the proportion of patients with recurrence of uveitis in the study eye within 36 months. In this study, a protocol-defined recurrence reflected the criteria outlined by the United States Food and Drug Administration (FDA) and included either an increase in vitreous haze $\geq$ 2 steps compared with baseline at any visit before 36 months or a deterioration in best-corrected visual acuity of $\geq$ 15 letters compared with baseline at any visit before month 36.

For suspected, nonprotocol-defined recurrences, investigators assumed a recurrence if a previously nonrecurrent study eye received "prohibited" local or systemic anti-inflammatory medication (i.e., systemic, injectable, topical corticosteroids, or systemic immunosuppressants) even when the criteria for a protocol-defined recurrence were not met. Any suspected recurrence that did not meet the protocol criteria was treated using standard of care therapies. Investigators also assumed a recurrence if a patient missed an ophthalmic assessment at 6-, 12-, or 36-month visits. To prevent postprocedural inflammatory reactions from being reported as uveitis recurrence, assessments for uveitis recurrence began after the day 7 visit.[11]

If a patient experienced a recurrence of uveitis in either eye that required treatment during the study, local treatment (intra- or peri-ocular corticosteroid injection) was used as the first-line therapy. Systemic immunosuppressant or steroid therapy was reserved for patients who failed local therapy. Patients who experienced a recurrence of uveitis were continued in the study; once the patient's recurrence was controlled, the local or systemic treatment regimen was discontinued after the established standard of care used for that specific regimen. Increase in anterior chamber cells with no increase in vitreous opacity was treated first with topical steroids.

All analyses were conducted using the Statistical Analysis Software (Statistical Analysis Software Institute, Inc) version 9.2

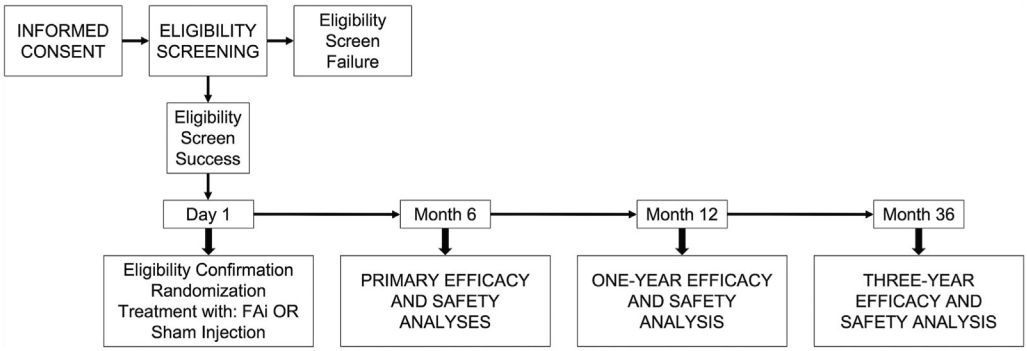

Figure 1. Study design. FAi = fluocinolone acetonide implant.

or higher. A continuity-corrected chi-square analysis was used to assess the statistical significance of the difference between treatment groups in the primary efficacy analysis. Descriptive statistics were used in exploratory efficacy analyses. Exploratory efficacy outcomes were described by the treatment group.

Results

A total of 153 patients were enrolled in the study; 101 eyes were randomized to the FAi-treated group and 52 to the treated sham group. All 153 patients were included in the intent-to-treat and safety populations, and 91 patients were included in the month 36 per protocol population (FAi-treated group, n = 67; treated sham group, n = 24). The most frequently reported reason for exclusion from the per protocol population for both treatment groups was that the patient had received prohibited or rescue medication at some time through month 36. All randomized patients received their intended treatment and were analyzed for primary outcomes. No patients were lost between screening and randomization, and patients were monitored from the baseline visit through 36 months. The study concluded per protocol at the end of the 36-month follow-up period. In total, 8 (5.2%) patients were lost to follow-up: (FAi-treated group, n = 5 [5.0%]; treated sham group, n = 3 [5.8%]). Six (3.9%) patients withdrew voluntarily (FAi-treated group, n = 4 [4.0%]; treated sham group, 2 [3.8%]), and 1 (0.7%) patient in the FAi-treated group discontinued because of investigator decision.

Baseline demographics and patient characteristics are shown in Table 1. In the FAi-treated group, there was a larger percentage of female patients, pseudophakic eyes, and eyes without vitreous haze than in the treated sham group.

Uveitis Recurrence

Over 36 months, eyes in the FAi-treated group had a significantly reduced recurrence rate when compared with those in the treated sham group (Table 2). At 36 months, 47 (46.5%) of 101 patients in the FAi-treated group had uveitis recurrence (including observed and suspected recurrences) compared with 39 (75.0%) of 52 patients in the treated sham group (Table 2). Both observed FDA-defined uveitis recurrences and suspected recurrences occurred in a greater percentage of the treated sham eyes than in the FAi-treated eyes (Table 3). A greater proportion of suspected recurrences were treated with systemic medications in the FAi-treated group than in the treated sham group (20/101 [19.8%] vs. 8/52 [15.4%], respectively); however, a lesser proportion of local injections were administered (2/101 [2.0%] vs. 13/52 [25.0%]) (Table 3).

At month 36, the median time to first recurrence was longer in the FAi-treated group than in the treated sham group (1116.0 days; 95% confidence interval, 847.00 to not evaluable days vs. 190.5 days; 95% confidence interval, 100.0–395.0 days, respectively). The probability of recurrence was higher in the treated sham group than in the FAi

Table 1. Baseline Demographics and Patient Characteristics

Characteristic	FAi (n = 101)	Treated Sham (n = 52)
Age, mean ± SD (yrs)	39.9 ± 12.9	40.6 ± 13.7
Sex (%)		
Female	62 (61.4)	18 (34.6)
Male	39 (38.6)	34 (65.4)
Systemic uveitis treatment (% eyes)	39 (38.6)	20 (38.4)
Corticosteroid therapy	37 (36.6)	19 (36.5)
Immunosuppressive therapy	2 (2.0)	1 (1.9)
Duration of uveitis, mean ± SD (yrs)	3.1 (3.0)	3.6 (3.0)
Vitreous haze absent (% eyes)	10 (9.9)	3 (5.8)
Vitreous haze grade (% eyes)		
0/0.5+	37 (36.6)	14 (27.0)
1/2+	64 (63.3)	38 (73.1)
3/4+	0	0
AC cells absent (% eyes)	67 (66.3)	33 (63.5)
AC cells grade (% eyes)		
0/0.5+	93 (91.3)	49 (94.1)
1/2+	8 (7.9)	3 (5.8)
3/4+	0	0
BCVA, mean ± SD (ETDRS letters)	66.4 (15.85)	63.6 (16.82)
CFT (% eyes)		
< 300 µm	70 (69.3)	36 (69.2)
≥ 300 µm	30 (29.7)	14 (26.9)
Lens status (% eyes)		
Pseudophakic	39 (38.6)	16 (30.8)
Phakic	61 (60.4)	34 (65.4)
IOP, mean ± SD (mmHg)	13.3 ± 3.07	13.1 ± 2.60

AC = anterior chamber; BCVA = best-corrected visual acuity; CFT = central foveal thickness; FAi = fluocinolone acetonide implant; IOP = intraocular pressure; SD = standard deviation.

Table 2. Proportion of Patients with Uveitis Recurrence in the Study Eye Per Time Point

Time Since Treatment	FAi (n = 101)	Treated Sham (n = 52)	Odds Ratio (95% CI)	P Value
6 mos	22 (21.8%)	28 (53.8%)	4.19 (2.04, 8.62)	< 0.001
12 mos	33 (32.7%)	31 (59.6%)	3.04 (1.52, 6.08)	0.002
36 mos	47 (46.5%)	39 (75.0%)	3.45 (1.65, 7.22)	0.001

CI = confidence interval; FAi = fluocinolone acetonide implant.

group throughout the study (Fig 2); these differences were significant at 6-, 12-, and 36-month time points (Table 2).

The mean (standard deviation) number of recurrences per eye occurring over 36 months was lower in the FAi-treated group than in the treated sham group (2.9 [4.63] vs. 4.2 [4.86], respectively), and a higher proportion of eyes in the FAi-treated group had no uveitis recurrence within 36 months than in the treated sham group (54/101 [53.5%] vs. 13/52 [25.0%]; confidence interval: 1.65−7.22; $P = 0.001$).

Adjunctive Treatments

At 36 months, the proportion of patients requiring systemic adjunctive treatment was similar between both groups (FAi: 32/101 [31.7%]; treated sham: 17/52 [32.7%]), with a greater proportion of patients in the treated sham group receiving local injection than in the FAi-treated group (treated sham: 27/52 [51.9%]; FAi: 9/101 [8.9%]) (Table 4). The proportions of patients receiving $\geq$ 1 adjunctive treatment during the study are summarized in Figure 3.

Visual Acuity Outcomes

At 36 months, the mean (standard deviation) change from baseline in best-corrected visual acuity letter score in the study eye was similar between treatment groups (+8.6 [13.55] for the FAi-treated group and +8.5 [12.42] for the treated sham group) (Fig 4). A similar proportion of patients gained $\geq$ 15 letters in the FAi-treated and treated sham groups (24/90 [26.7%] and 12/44 [27.3%] patients, respectively).

Control of Edema

Thirty-three study eyes in the FAi-treated group and 13 study eyes in the sham group had macular edema at baseline (as determined by the investigators' evaluation of all available clinical information, including OCT). At month 36, there was a tendency for fewer eyes in the FAi-treated group to have macular edema than treated sham eyes (8/33 [24.2%] vs. 6/13 [46.2%], respectively) (Fig 5). Although the mean (standard deviation) central foveal thickness as measured by OCT was slightly higher at baseline in the FAi-treated group (262.1 [144.04] vs. 254.4 [135.55] μm, respectively), a lower central foveal thickness was observed from month 12 onward in the FAi-treated group than in the treated sham group (Fig 6).

Vitreous Haze

A larger proportion of eyes in the FAi-treated group had no vitreous haze at 36 months than treated sham eyes (86/90 [95.6%] vs. 37/44 [84.1%], respectively). The proportion of eyes with no vitreous haze at baseline was slightly higher in the FAi-treated group than in the treated sham group (10/101 [9.9%] vs. 3/52 [5.8%], respectively; Table 1) and remained so at all post-treatment time points.

Safety: IOP and Cataract

Overall, IOP was well controlled in both the FAi-treated and treated sham groups (Fig 7). More events of IOP elevation were reported in the FAi-treated group than in the treated sham group: IOP of > 25 mmHg occurred in 23.8% versus 3.8% of FAi-treated and treated sham eyes, respectively, and IOP of > 30 mmHg occurred in 16.8% versus 1.9% in FAi-treated versus treated sham eyes, respectively (Table 5). Most IOP elevations were treated with IOP-lowering medications; 75 (74.3%) of 101 of eyes in the FAi-treated group received IOP-lowering medication compared with 38 (73.1%) of 52 of eyes in the treated sham group. In the treated sham group, mean IOP was slightly lower than baseline at 36 months. There was no meaningful difference

Table 3. Recurrences and Reasons for Suspecting a Uveitis Recurrence

Recurrence and Reason for Event	FAi (n = 101)	Treated Sham (n = 52)
Recurrence rate within 36 mos, n (%)	47 (46.5)	39 (75.0)
Observed	19 (18.8)	15 (28.8)
Suspected	28 (27.7)	24 (46.2)
Reason for suspected event, n (%)		
Missing data	6 (5.9)	3 (5.8)
Systemic corticosteroid or immunosuppressant	20 (19.8)	8 (15.4)
Intraocular/peri-ocular corticosteroid	2 (2.0)	13 (25.0)
Topical corticosteroid	54 (53.5)	13 (25.0)

FAi = fluocinolone acetonide implant.

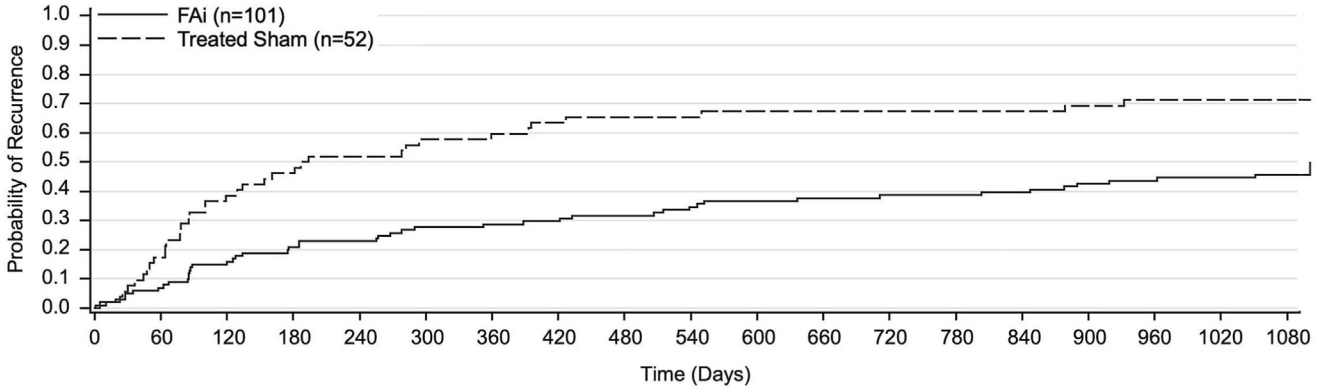

Figure 2. Probability of uveitis recurrence by days from treatment. FAi = fluocinolone acetonide implant.

in the percentage of eyes requiring IOP-lowering surgery over 36 months between the FAi-treated group and the treated sham group (2/101 [2.0%] vs. 0/52 [0%], respectively).

Additionally, as expected, cataract surgery was required more frequently over 36 months in the FAi-treated group than in the treated sham group (43/101 [70.5%] vs. 9/52 [26.5%], respectively) (Table 5). There were more adverse events (AEs) of cystoid macular edema reported in the FAi-treated group (8/52 [15.4%]) versus treated sham (4/101 [4.0%]), which could be associated with the frequent cataract surgeries that occurred in the FAi-treated group.

Safety: Hypotony AEs

Adverse events of hypotony, a known complication of uveitis, were typically transient and associated with the injection procedure. Of the 10 (9.9%) events of hypotony in FAi-treated eyes, 6 were considered to be possibly related to treatment, and 4 were probably related. No events of hypotony were reported in the treated sham group.

Table 4. Number of Adjunctive Treatments by Type of Treatment

	Within 36 Mos	
Number of Treatments	*FAi (n = 101)*	*Treated Sham (n = 52)*
≥ 1 local injection*	9 (8.9%)	27 (51.9%)
1 injection	5	15
2 injections	2	5
3 injections	1	3
4 injections	—	2
5 injections	1	2
> 5 injections	—	—
≥ 1 systemic treatment†	32 (31.7%)	17 (32.7%)
1 treatment	14	7
2 treatments	8	2
3 treatments	1	4
4 treatments	4	1
5 treatments	2	1
> 5 treatments	3	2

FAi = fluocinolone acetonide implant.
*Adjunctive intra/peri-ocular steroid.
†Patients received ≥ 1 course of systemic steroid or immunosuppressant adjunctive treatment.

Discussion

This phase III, prospective, randomized, controlled, 36-month multicenter study in Indian patients with NIU-PS demonstrated the effectiveness of the 0.2-μg/day FAi to improve the management of uveitis, increasing the time to first recurrence, decreasing the number of recurrences, maintaining or improving visual acuity, and minimizing macular edema. Although the 0.2-μg/day FAi has been studied under a similar protocol,[11] the current analysis, conducted at study sites in India, expands these assessments to a new population.

These long-term results confirm the previously reported 6-, 12-, 24-, and 36-month results[11,12] and demonstrate that uveitis recurrence rates among FAi-treated eyes were significantly reduced compared with treated sham eyes over the entire 36 months of the study ($P < 0.001$, $P = 0.002$, and $P = 0.001$ at 6, 12, and 36 months, respectively). Most notably, there were far fewer observed FDA-defined recurrences in the FAi-treated group than in the treated sham group, supporting the beneficial effect of treatment with the 0.2-μg/day FAi.

Moreover, the rate of suspected recurrence, based on missing data or use of local or systemic corticosteroid or immunosuppressants, was also substantially lower in the 0.2-μg/day FAi group than in the treated sham group (27.7% vs. 46.2%). These data align with the results from previous studies that led to the FDA approval of the 0.2-μg/day FAi for the treatment of NIU-PS.[11] Additionally, more than half (53.5%) of FAi-treated eyes remained free of recurrence for 36 months compared with 25.0% of eyes in the treated sham group. Overall, the decreased number of uveitis recurrences—as well as the delayed median time to first recurrence—in the FAi-treated group suggest better uveitis control with the 0.2-μg/day FAi than standard treatments. Unfortunately, for this analysis, there are no direct comparative data for other injectable delivery systems.

Furthermore, the suspected recurrences were very conservatively assessed: missed appointments and fellow-

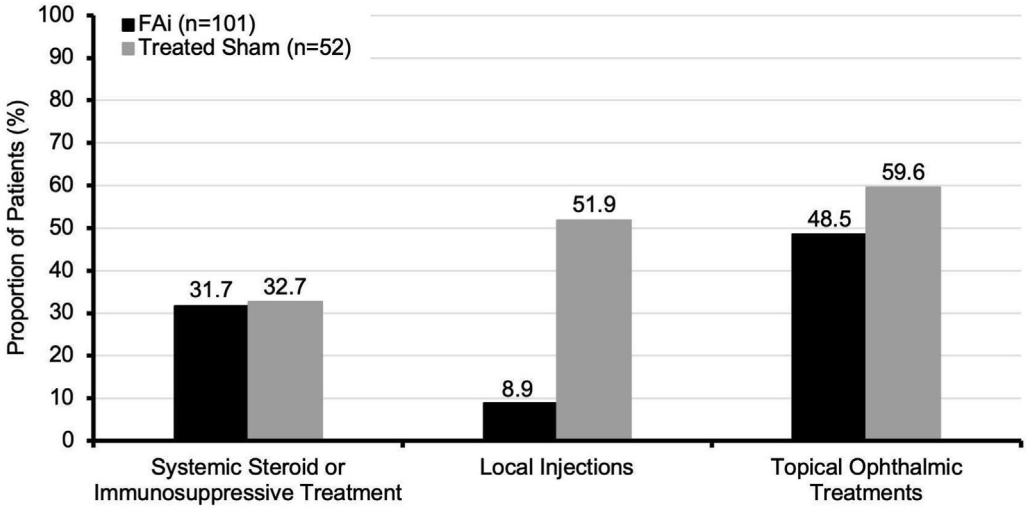

Figure 3. Proportion of patients receiving ≥ 1 adjunctive treatment (systemic treatment, local injections, or topical ophthalmic treatment) over 36 months. FAi = fluocinolone acetonide implant.

eye treatments were both included in the criteria, which may have led to overestimation of actual recurrences in the FAi-treated group, in which 4 patients had a missed visit compared with no treated sham patients. Additionally, 6 patients (5.9%) in the FAi-treated group and 3 patients (5.8%) in the treated sham group were considered to have suspected recurrence because of missing data.

Another measure of uveitis disease control after the 0.2-μg/day FAi is the need for adjunctive treatment. In the FAi-treated group, a higher proportion of eyes received topical corticosteroids, which may be related to the number of pseudopakic eyes in the FAi-treated group, because topical corticosteroid use is common after lens replacement. This differs from a previous study in which there was a much higher use of systemic therapy in the FAi-treated group than in the treated sham, although topical corticosteroid use was comparable between the 2 groups. The reasons for these differences between treatment groups and between studies are not entirely clear and warrant further investigation.[11]

According to one study, the most common form of uveitis in India was anterior uveitis (35.22%) followed by intermediate (30.11%), posterior (25%), and panuveitis (9.65%).[13] Additionally, the most common forms of NIU reported were intermediate (31.9%), posterior (18.2%), and panuveitis (17.6%). Considering the differences observed between ethnicities in the patterns of uveitis cases, it is possible that patient ethnicity may be a contributing factor to the differences in response to the 0.2-μg/day FAi in this study and that reported by Jaffe et al.[11]

Among patients receiving the 0.2-μg/day FAi, fewer were treated with additional intraocular corticosteroids compared with the treated sham group. Although these data coincide with other measures of disease control assessed in this study, they may have long-term implications. A common concern in uveitis management is the need for patients to return to the

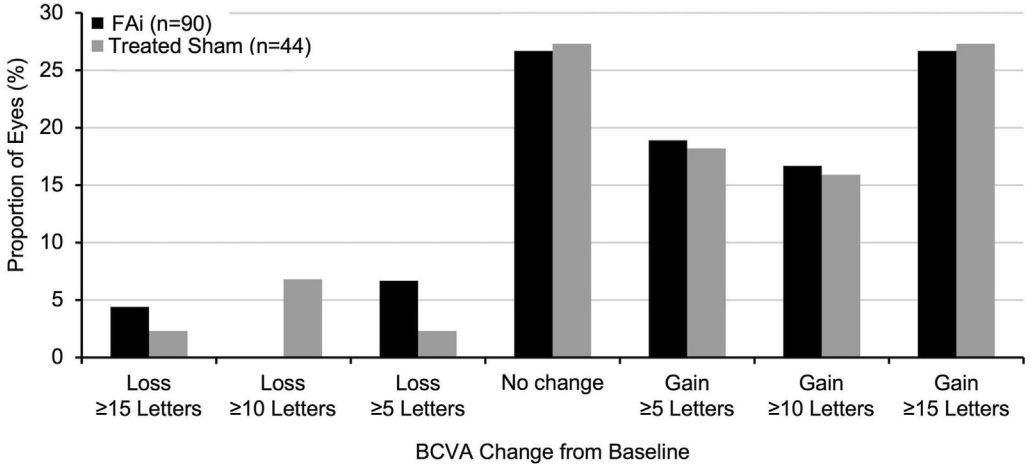

Figure 4. Changes in best-corrected visual acuity (BCVA) from baseline at 36 months. FAi = fluocinolone acetonide implant.

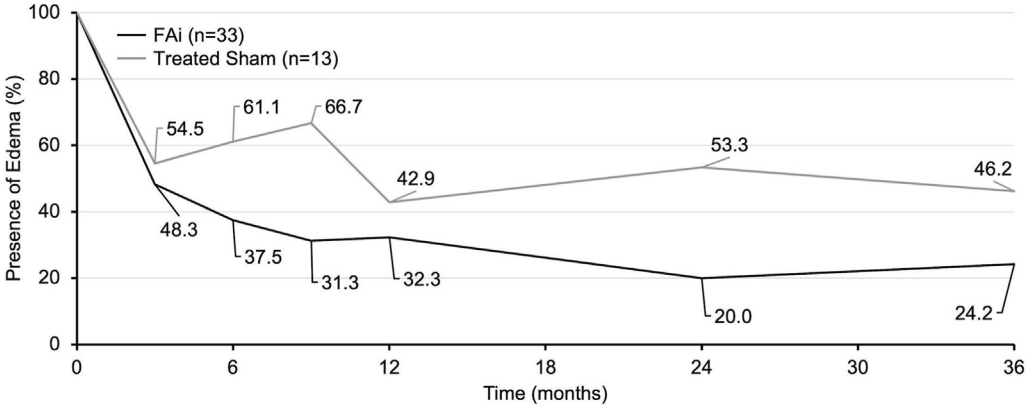

Figure 5. Presence of macular edema by months from treatment. FAi = fluocinolone acetonide implant.

clinics for additional injections. The need for these treatments and associated office visits increases patient and provider burden. Additionally, the adjunctive medications themselves are associated with their own side effect profiles. By reducing the need for intraocular corticosteroid injections, the 0.2-μg/day FAi may prove to decrease these burdens.

In addition to the reduced use of adjunctive treatment, FAi-treated eyes largely maintained or showed an improvement in visual acuity, although these data were similar to those in the treated sham group. Fluocinolone acetonide implant-treated eyes also displayed an improvement in macular edema when compared with treated sham eyes. Although both the groups had sustained reductions of macular edema (as assessed by central foveal thickness) over 36 months, macular edema in the FAi-treated group was significantly reduced starting from 12 months through the end of the study compared with the treated sham group. Additionally, fewer FAi-treated eyes had any edema at 36 months than treated sham eyes.

An important concern with ocular corticosteroid use is increased IOP. Here, IOP events had a higher occurrence in the FAi-treated group but were generally well controlled in both the study groups; most frequently, IOP-lowering medications were used to control IOP elevations, and their rates of use were comparable between the FAi and treated sham groups. These results differ from a previous study of the 0.2-μg/day FAi to treat NIU-PS, where a much lower proportion of patients received IOP-lowering medication,[11] but between-study differences in population and medical practices (United States, United Kingdom, Germany, Hungary, Israel, and India vs. India alone) likely account for these discrepancies. Overall, in this study, IOP was managed primarily with topical IOP-lowering drugs and, in a small number of cases, with surgical intervention.

Rates of IOP-lowering surgery were low in both FAi-treated and treated sham eyes (2.0% and 0%, respectively). This contrasts with previous studies of the 0.59-mg fluocinolone acetonide IVT implant (RETISERT, Bausch and Lomb): within 1 year, 10.9% of eyes treated with the 0.59-mg FAi required IOP-lowering surgery and 32.0% required surgery within 3 years.[14] In a case series comparing the DEX IVT implant with the 0.59-mg FAi, DEX was associated with similar rates of IOP-lowering surgery as the 0.2-μg/day FAi over up to 2 years.[15,16] It is likely that lower rates of IOP-lowering surgery in FAi-treated eyes is related to the lower daily steroid dose provided by the 0.2-μg/day FAi compared with the 0.59-mg FAi. Additionally, the 0.2-μg/day FAi is placed further away from the iris and trabecular meshwork, which may contribute to fewer IOP elevation events after FAi insertion.

Along with IOP elevations, corticosteroids are associated with increased incidence of cataract. In the current study, the

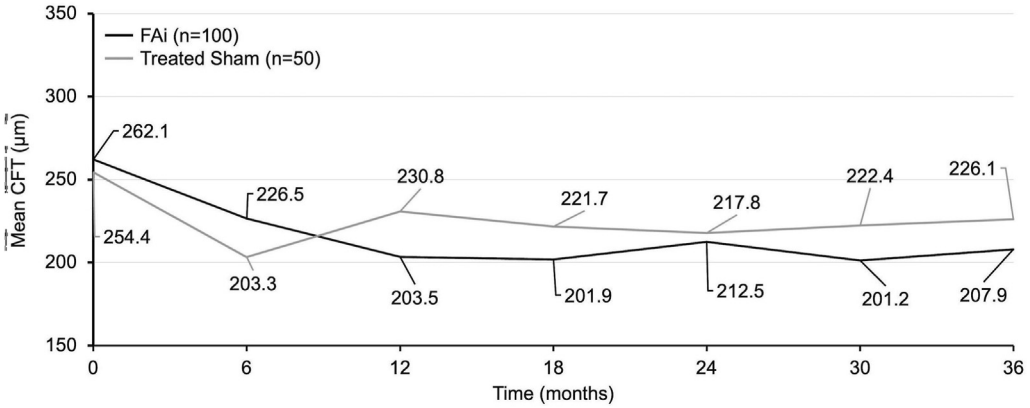

Figure 6. Mean central foveal thickness (CFT) over 36 months. FAi = fluocinolone acetonide implant.

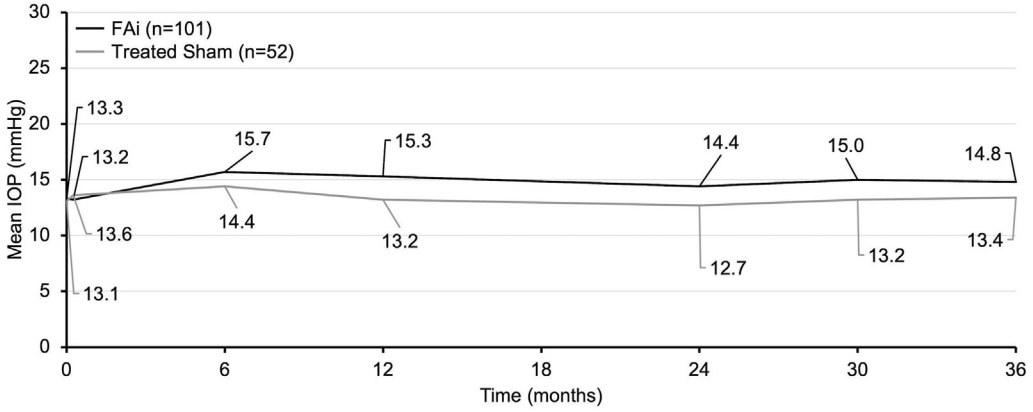

Figure 7. Mean intraocular pressure (IOP) over 36 months. FAi = fluocinolone acetonide implant.

cataract surgery rate was higher in the FAi-treated group than in the treated sham group (70.5% and 26.5%, respectively). These rates are comparable with those in the previous studies of FAi, one for the treatment of NIU-PS (73.8% and 23.8%, respectively) and another for diabetic macular edema (80.0% and 27.3%, respectively).[11,17] Studies of the 0.59-mg FAi to treat NIU-PS have described similarly higher proportions of baseline-phakic eyes requiring cataract extraction at the end of the study.[18] During a 6-month study of DEX in NIU-PS, 15% of phakic DEX-treated eyes reported cataract compared with 7% of control-treated eyes[19]; in the current study, 4.9% of FAi-treated phakic study eyes and 3.6% of treated sham eyes required cataract extraction at 6 months. Collectively, these data indicate that the risk of cataract formation and extraction resulting from the continuous, long-term, submicrogram corticosteroid exposure secondary to the 0.2-μg/day FAi is similar to the risk from other comparable corticosteroid implants.

Table 5. IOP-related Events Through 36 Months

Event	36 Mos	
	FAi (n = 101)	*Treated Sham (n = 52)*
IOP (mmHg)		
Mean (SD)	14.8 (6.46)	13.4 (3.01)
Change from baseline (SD)	1.4 (6.78)	0.4 (3.70)
IOP events, n (%)		
> 25 mmHg	24 (23.8)	2 (3.8)
> 30 mmHg	17 (16.8)	1 (1.9)
Change from baseline ≥ 12 mmHg	28 (27.7)	4 (7.7)
IOP-lowering medication	75 (74.3)	38 (73.1)
IOP-lowering surgery	2 (2.0)	0
Hypotony	10 (9.9)	0
Cataract		
Phakic at baseline, n	61	34
Cataract surgeries,* n (%)	43 (70.5)	9 (26.5)

FAi = fluocinolone acetonide implant; IOP = intraocular pressure; SD = standard deviation.
*Percentages based on the number of study eyes with phakic lens status at baseline.

The rate of hypotony events in this study was consistent with previous work (approximately 10%).[11] Based on these data, the risk of hypotony after the 0.2-μg/day FAi does not outweigh the treatment benefits of the 0.2-μg/day FAi in NIU-PS.

Interestingly, the data from the current study are exemplified by smaller case series in which the total number of local corticosteroid injections was significantly reduced, patients experienced significant or numerically improved best-corrected visual acuity, and central retinal thickness was decreased within 2 years after the 0.2-μg/day FAi.[20,21]

As with any clinical trial, this study has certain limitations. First and foremost, eyes were not categorized based on the anatomic subtype of uveitis present (e.g., intermediate, posterior, or panuveitis), so the relative efficacy of the 0.2-μg/day FAi in different uveitis subtypes was not evaluated. Furthermore, the study likely did not have sufficient power to detect significant efficacy differences based on the underlying uveitis etiology, had that data been available, because the study was originally designed and powered to investigate differences in uveitis recurrence at 6 months. Masking of investigators during the study may have also been challenged by the possibility of detecting the implant on fundus examination. Notwithstanding these limitations, the current study data on the 0.2-μg/day FAi are largely consistent with previous work in terms of clinical assessments, and discrepancies in use of particular adjunctive treatments are easily attributable to causes unrelated to the 0.2-μg/day FAi itself.[11]

This long-term study demonstrates that the 0.2-μg/day FAi is associated with a reduction of uveitis recurrence, increase in time to first recurrence, and reduction of macular edema while maintaining or improving visual acuity in patients with NIU-PS. Additionally, the 0.2-μg/day FAi is associated with a reasonable safety profile in relation to the incidence of AEs, IOP-related events, and incidence of cataract compared with higher doses of FAi; this suggests that the 0.2-μg/day FAi dose provides an equivalent

duration of action with fewer observed AEs compared with the higher dose. Taken together, this study indicates that the 0.2-μg/day FAi provides improved disease control and, therefore, patient outcomes in NIU-PS.

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HUMAN SUBJECTS: Human subjects were included in this study.

The institutional review board at each center approved the study; these institutional review boards were located at LV Prasad Eye Institute (Hyderabad, India), Sri Sankaradeva Nethralaya (Guwahati, India), Regional Institute of Ophthalmology (Patna, India), CH Nagri Eye Hospital (Ahmedabad, India), King Edward Memorial Hospital and Seth Gordhandas Sunderdas Medical College (Mumbai, India), Deenanath Mangeshkar Hospital and Research Center (Pune, India), PBMA's HV Desai Eye Hospital (Pune, India), Dr. Shroff`s Charity Eye Hospital (New Delhi, India), Sankara Nethralaya (Chennai, India), Vasan Eye Care Hospital (Chennai, India), Sri Ramachandra Hospital (Chennai, India), JL Rohatgi Eye Hospital (Kanpur, India), King George's Medical University (Uttar Pradesh, India), ICARE Eye Hospital & Post Graduate Institute (Noida, India), and the Regional Institute of Ophthalmology (Kolkata, India). The study was performed in accordance with the Declaration of Helsinki, and all patients provided written informed consent before enrollment.

No animal subjects were used in this study.

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Analysis and interpretation: Biswas, Tyagi, Agarwal.

Obtained funding: N/A

Overall responsibility: Biswas, Tyagi, Agarwal.

Abbreviations & Acronyms:
AE = adverse event; **DEX** = dexamethasone; **FAi** = fluocinolone acetonide implant; **FDA** = Food and Drug Administration; **IOP** = intraocular pressure; **IVT** = intravitreal; **NIU** = noninfectious uveitis; **PS** = posterior segment.

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